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EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

pat-dept@quarles.com

Office Action Summary	Application No.	Applicant(s)	
	10/688,416	SCHWARTZ ET AL.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-94* is/are pending in the application.

4a) Of the above claim(s) *71-94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on April 16, 2008 is acknowledged and has been entered. Claims 1, 10-11, 25, 32, 46-48, 51 and 69-70 have been amended. Claims 71-94 are withdrawn. Claims 1-70 are pending.

Claims 1-70 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made FINAL.

Priority

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/419,884 and the disclosure of the prior patents, 5,720,928, 6,294,136, and 6,610,256, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Claims 10-16, 32-38 and 50-56 recite the claim limitation "periodically reversing the flow to cause the polymeric molecules to hover in an elongated/aligned or separated state". This claim limitation does not have support in the disclosures of the applications or patents to which priority is claimed. The claims are being granted the filing date of the instant application, October 17, 2003.

Previous Rejections

The priority for claims 49-70 is withdrawn in view of Applicant's arguments regarding the support in the provisional application 60/419884. Therefore, the claims are awarded the priority of the provisional application.

Double Patenting

1. Claim 1, 4-7, 17, 25, 28-31, 39, 45-47 and 48 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 7,049,074, issued May 23, 2006 ('074 patent herein). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 1 of the '074 patent is directed to a method of elongating and fixing a nucleic acid molecule on a planar surface coated with a positively charged substance and the density of said positively charged substance is sufficient that nucleic acid molecule is fixed and elongated along

its length on the planar surface. Claim 1, 25 and 48 of the instant application are drawn to a method of elongating, aligning or separating polymeric molecules comprising multiple steps, including placing the polymeric molecules in a carrier liquid, passing the molecules and liquid through a microchannel comprising a wall and controlling the elongation/alignment or separation of polymeric molecule through control of laminar flow and causing the molecule to adhere in a straightened configuration to the wall. Claims 4-7, 23-24, 29-31 and 45-47 of the instant application are directed to applying restricting enzymes or a second polymeric molecule to the straightened polymer and include steps of optical inspection of the polymer. The limitations disclosed in independent claims 1, 25 and 48 in combination with the absorption and elongation of the polymeric molecule of claim 17 and 39, and in view of the reactions of claims 4-7, 23-24, 29-31 and 45-47, are disclosed generally in the method of claim 1.

While the claims are not identical, the methods comprise straightening polymeric molecules generically (or nucleic acids specifically in the '074 patent) through fixing the polymers through electrostatic attraction between the polymer and the surface. In the '074 patent, the surface is planar and comprises a positively charged substance, while the instant application comprises a microchannel with a wall surface. The claims of the instant application and the '074 patent address a similar scope and breadth of a method of fixing and straightening of polymers or nucleic acids such that the claims of the instant application are obvious over the claims of the '074 patent.

2. Claims 1, 3, 4-7, 17, 23-25, 27-31, 39, 45-48 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 10, 12-13, 15-16, and

26-27 of U.S. Patent No. 6,509,158, issued January 2003 ('158 patent herein). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 1 of the '158 patent is directed to a method of characterizing a nucleic acid molecule comprising imaging the nucleic acid molecule, which is elongated and fixed along its length on a solid planar surface so that said nucleic acid molecule is individually accessible to enzymatic reactions. Claim 1, 25 and 48 of the instant application are drawn to a method of elongating, aligning or separating polymeric molecules comprising multiple steps, including placing the polymeric molecules in a carrier liquid, passing the molecules and liquid through a microchannel comprising a wall and controlling the elongation/alignment or separation of polymeric molecule through control of laminar flow and causing the molecule to adhere in a straightened configuration to the wall. Claims 4-7, 23-24, 29-31 and 45-47 of the instant application are directed to applying restricting enzymes or a second polymeric molecule to the straightened polymer and include steps of optical inspection of the polymer.

While the claims are not identical, the methods comprise straightening polymeric molecules generically (or nucleic acids specifically in the '158 patent) through fixing the polymers through electrostatic attraction between the polymer and the surface. In the '158 patent, the surface is planar while the instant application comprises a microchannel with a wall surface. The claims of both patents are also directed to optical or imaging analysis of the straightened polymers and include enzymatic analysis. The claims of the instant application and the '158 patent address a similar scope and breadth of a method of fixing and straightening of polymers or nucleic acids such that the claims of the instant application are obvious over the claims of the '158 patent.

Claim Rejections - 35 USC § 102

3. Claims 1-7, 25-31, 48 and 62-64 are rejected under 35 U.S.C. 102(b) as being unpatentable over Kambara (US Patent 5,356,776; October 1994) in view of Bensimon et al. (US Patent 6,256,153; July 2001; filed February 10, 1995). Kambara teaches a method of fixing and straightening DNA molecules in a channel (Abstract).

With regard to claim 1, Kambara teaches a method for elongating polymeric molecules comprising the steps of:

(a) passing a polymeric molecule in a laminar-flowing liquid through a micro-channel sized to provide laminar flow of the liquid along a micro-channel length (col. 3, lines 48-57, where the terminus of the DNA is fixed and stretched via fluid flow; col. 4, lines 1-17, where the passage is passable by DNA but not the particle and would therefore meet the limitation of microchannel; see Example 4, col. 10, lines 48-65, where the dimensions of the channel are provided; liquid flow is used to fix the particle and stretch the DNA); and

(b) controlling the flow of liquid to cause elongation of the polymeric molecule within the laminar flow (col. 3, lines 48-57, where the terminus of the DNA is fixed and stretched via fluid flow; col. 4, lines 1-17; liquid flow is used to fix the particle and stretch the DNA).

With regard to claim 25, Kambara teaches a method for aligning polymeric molecules comprising the steps of: (a) passing a plurality of polymeric molecules in a laminar-flowing liquid through a micro-channel sized to provide laminar flow of the liquid along a micro-channel length (col. 3, lines 48-57, where the terminus of the DNA is fixed and stretched via fluid flow; col. 4, lines 1-17, where the passage is passable by DNA but not the particle and would therefore

meet the limitation of microchannel; see Example 4, col. 10, lines 48-65, where the dimensions of the channel are provided; liquid flow is used to fix the particle and stretch the DNA); and (b) controlling the flow of liquid to cause alignment of the polymeric molecules within the laminar flow (col. 3, lines 48-57, where the terminus of the DNA is fixed and stretched via fluid flow; col. 4, lines 1-17; liquid flow is used to fix the particle and stretch the DNA).

With regards to claim 48, Kambara teaches a method for separating polymeric molecules of differing molecular weight comprising the steps of:
(a) passing polymeric molecules in a laminar-flowing liquid through a micro-channel sized to provide laminar flow of the liquid along a micro-channel length (col. 3, lines 48-57, where the terminus of the DNA is fixed and stretched via fluid flow; col. 4, lines 1-17, where the passage is passable by DNA but not the particle and would therefore meet the limitation of microchannel; see Example 4, col. 10, lines 48-65, where the dimensions of the channel are provided; liquid flow is used to fix the particle and stretch the DNA); and
(b) controlling the laminar flow of liquid to separate the polymeric molecules of differing molecular weights within the laminar flow (col. 3, lines 48-57, where the terminus of the DNA is fixed and stretched via fluid flow; col. 4, lines 1-17; liquid flow is used to fix the particle and stretch the DNA).

With regard to claim 2, 26, Kambara teaches an embodiment of claim 1, 25, wherein the micro-channel has a cross-sectional dimension within one order of magnitude of a relaxed diameter of the polymeric molecule (see Example 4, col. 10, lines 48-65, where the dimensions of the channel are provided).

With regard to claim 3, 27, 64, Kambara teaches an embodiment of claim 1, 25, 48, wherein the micro-channel includes a transparent wall and including the step of optically analyzing the elongated polymeric molecule suspended within the laminar flow (Example 4, col. 10, where following stretching in the microchannel, the DNA is optically inspected to determine the position of the label at the opposite end of the molecule, see especially lines 65-67).

With regard to claim 4, 28, Kambara teaches an embodiment of claim 1, 25, including the step of reacting the elongated polymeric molecule suspended within the laminar flow with a reactant (Example 4, col. 9, line 59 to col. 11, line 25, where labeled probes are hybridized to the DNA, the DNA is oriented using the apparatus and a detailed DNA map is obtained, see Figure 7).

With regard to claim 6, 30, 62, Kambara teaches an embodiment of claim 4, 28, 60, wherein the reactant is a second polymeric molecule reacting with at least one elongated polymeric molecule (Example 4, col. 9, line 59 to col. 11, line 25, where labeled probes are hybridized to the DNA, the DNA is oriented using the apparatus and a detailed DNA map is obtained, see Figure 7).

With regard to claim 7, 31, 63, Kambara teaches an embodiment of claim 6, 25, 57, wherein the polymeric molecules are DNA (Abstract, where the polymeric molecules that are stretched are DNA molecules).

With regard to claim 5, 29, Kambara teaches an embodiment of claim 4, 28, wherein the reactant is an enzyme causing cleavage of the polymeric molecule (Example 1, col. 6, line 20-26, where the DNA is digested with a restriction endonuclease).

Claim Rejections - 35 USC § 103

4. Claims 8-9, 17-18, 21-24, 39-40, 43-46 and 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kambara et al. (US Patent 5,356,776; October 1994) as applied to claims 1-7, 25-31, 48 and 62-64 and further in view of Bensimon et al. (US Patent 6,256,153; July 2001). Kambara teaches a method of fixing and straightening DNA molecules in a channel (Abstract).

Kambara teaches the limitations of claims 1-7, 25-31, 48 and 62-64 as recited in the 102 rejection stated above. However, Kambara does not teach the step of aligning or staging molecules within the passage or channel or that the wall is electrostatically attractive to the DNA molecule. Bensimon teaches a process for aligning a macromolecule onto the surface of a support comprising fixing one end onto the surface (Abstract).

With regard to claim 8, Bensimon teaches an embodiment of claim 1, wherein multiple polymeric molecules are simultaneously passed through the channel (col. 17, Example 1, lines 18-23, where the total number of molecules of fluorescence-labeled λ DNA was added in different buffers, wherein this constitutes multiple polymeric molecules simultaneously passed through the channel).

With regard to claim 9, Bensimon teaches an embodiment of claim 1, including the step of staging the polymeric molecule with a plurality of other polymeric molecules in the liquid before passage through the channel (col. 17, Example 1, lines 18-23, where the total number of molecules of fluorescence-labeled λ DNA was added in different buffers, wherein this constitutes multiple polymeric molecules simultaneously passed through the channel).

With regard to claims 17 and 39. Bensimon teaches an embodiment of claim 1, 25, wherein at least a first wall of the micro-channel provides attraction to the polymeric molecule and further including the step of: (c) adsorbing of the polymeric molecule to the first wall of the micro-channel in straightened form (col. 3, lines 58-65, where the adsorption of the macromolecule onto the surface can be controlled through surface charges and the electrostatic interactions between the surface and the molecule; col. 4, lines 52-61, where specific types of surface functionalities are described; see also col. 5, lines 4-23, for example; and see Example 1, col. 17, lines 39-46, where capillary force on the DNA molecule(s) is sufficient to stretch the molecule; col. 4, lines 4-6, where it is noted that one aligned, the molecules adhere strongly to the surface).

With regard to claim 18, 40, Bensimon teaches an embodiment of claim 17, 39 wherein step (c) includes the steps of controlling the flow rate of the liquid and the size of the micro-channel to cause adsorption by random encounters between at least one end of the polymeric molecule and a wall of the micro-channel (col. 3, lines 58-65, where the adsorption of the macromolecule onto the surface can be controlled through surface charges and the electrostatic interactions between the surface and the molecule; col. 4, lines 52-61, where specific types of surface functionalities are described; see also col. 5, lines 4-23, for example; and see Example 1, col. 17, lines 39-46, where capillary force on the DNA molecule(s) is sufficient to stretch the molecule; col. 4, lines 4-6, where it is noted that one aligned, the molecules adhere strongly to the surface).

With regard to claim 21, 43, 58, Bensimon teaches an embodiment of claim 17, 39, 57 wherein the micro-channel includes an elastic channel material releasably adhered to an optical

mapping surface to create the micro-channel between the elastic material and the optical mapping surface and wherein the adsorption is to the optical mapping surface (Example 3, col. 19, lines 21-26, where the coverslip is removed from the adhered molecules).

With regard to claim 22, 44, 59, Bensimon teaches an embodiment of claim 21, 43, 58, further including the step of separating the elastic channel material from the optical mapping surface after adsorption of the polymeric molecule to the optical mapping surface (Example 3, col. 19, lines 21-26, where the coverslip is removed from the adhered molecules).

With regard to claim 23, 45, 60, Bensimon teaches an embodiment of claim 17, 39, 57, further including the step of reacting the adsorbed polymeric molecule with a reactant (col. 9, lines 29-60, where the polymeric molecule within the laminar flow may be reacted with a variety of reactants, including DNA, RNA or proteins through hybridization or labeling; col. 12, lines 53-63, where the position of specific genes on genomic DNA are determined by hybridization with gene specific probes).

With regard to claim 24, 46, 61, Bensimon teaches an embodiment of claim 23, 45, 60, wherein the reactant is an enzyme causing cleavage of the polymeric molecule (col. 12, lines 53-58, where the polymer is genomic DNA and can be cleaved with restriction enzyme prior to further 'physical mapping' steps).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the teachings of Bensimon to the method of DNA stretching and analysis taught by Kambara to arrive at the claimed invention with a reasonable expectation for success. Kambara teaches a method comprising affixing one end of a DNA molecule to a bead, which comprises a broad interpretation of a wall of a channel, places the DNA in a channel

that captures the wall of the channel and stretches the DNA using fluid flow, or laminar flow. Bensimon teaches a very similar method of DNA analysis, however in this case an end of the DNA is fixed and the DNA is aligned along the length of a wall, which may comprise a bead (col. 3, lines 11-17, where the support of Bensimon can take many forms, including beads or particles), through progress of a meniscus instead of by laminar flow. Therefore, as each of these elements were known in the prior art at the time of the invention and the combination of these elements would provide a predictable result, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have incorporated these elements to analyze straightened DNA molecules.

5. Claims 10-16, 20, 32-38, 42, 49-57, 65-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kambara et al. (US Patent 5,356,776; October 1994) in view of Bensimon et al. (US Patent 6,256,153; July 2001) as applies to claims 8-9, 17-18, 21-24, 39-40, 43-46 and 58-61 and 58-64 above and further in view of Chen et al. (US Patent 6,762,059; July 2004). Kambara teaches a method of fixing and straightening DNA molecules in a channel (Abstract).

With regard to claim 12, 34, 52, Kambara teaches an embodiment of claim 10, 32, 50, wherein the micro-channel includes a transparent wall and including the step of optically analyzing the elongated polymeric molecule as it hovers within the laminar flow (Example 4, col. 10, where following stretching in the microchannel, the DNA is optically inspected to determine the position of the label at the opposite end of the molecule, see especially lines 65-67).

With regard to claim 13, 35, 53, Kambara teaches an embodiment of claim 10, 32, 50, including the step of reacting the elongated polymeric molecule hovering within the laminar flow

with a reactant (Example 4, col. 9, line 59 to col. 11, line 25, where labeled probes are hybridized to the DNA, the DNA is oriented using the apparatus and a detailed DNA map is obtained, see Figure 7).

With regard to claim 14, 36, 54, Kambara teaches an embodiment of claim 13, 35, 53, wherein the reactant is an enzyme causing cleavage of the polymeric molecule (Example 1, col. 6, line 20-26, where the DNA is digested with a restriction endonuclease).

With regard to claim 15, 37, 55, Kambara teaches an embodiment of claim 13, 35, 53, wherein the-reactant is a second polymeric molecule (Example 4, col. 9, line 59 to col. 11, line 25, where labeled probes are hybridized to the DNA, the DNA is oriented using the apparatus and a detailed DNA map is obtained, see Figure 7).

With regard to claim 16, 38, 56, Kambara teaches an embodiment of claim 15, 35, 55, wherein the polymeric molecules are DNA (Abstract, where the polymeric molecules that are stretched are DNA molecules).

With regards to claim 69, Kambara teaches an embodiment of claim 48 wherein the micro-channel has a cross-sectional dimension within one order of magnitude of a relaxed diameter of the polymeric molecule (see Example 4, col. 10, lines 48-65, where the dimensions of the channel are provided).

While Kambara teaches the limitations of the claims above, Kambara does not teach the limitations of claims 57 or 66. Bensimon teaches a process for aligning a macromolecule onto the surface of a support comprising fixing one end onto the surface (Abstract).

With regards to claim 57, Bensimon teaches an embodiment of claim 49 further including the step of fixing the separated polymeric molecules to a substrate after their separation (col. 3,

lines 58-65, where the adsorption of the macromolecule onto the surface can be controlled through surface charges and the electrostatic interactions between the surface and the molecule; col. 4, lines 52-61, where specific types of surface functionalities are described; see also col. 5, lines 4-23, for example; and see Example 1, col. 17, lines 39-46, where capillary force on the DNA molecule(s) is sufficient to stretch the molecule; col. 4, lines 4-6, where it is noted that one aligned, the molecules adhere strongly to the surface).

With regards to claim 66, Bensimon teaches an embodiment of claim 65 further including the step of fixing the elongated polymeric molecules to a substrate (col. 3, lines 58-65, where the adsorption of the macromolecule onto the surface can be controlled through surface charges and the electrostatic interactions between the surface and the molecule; col. 4, lines 52-61, where specific types of surface functionalities are described; see also col. 5, lines 4-23, for example; and see Example 1, col. 17, lines 39-46, where capillary force on the DNA molecule(s) is sufficient to stretch the molecule; col. 4, lines 4-6, where it is noted that one aligned, the molecules adhere strongly to the surface).

Regarding claims 12-16, 34-38, 52-56, Bensimon does not teach the limitations of claims 10-11, 32-33, 50-51, wherein the flow of the polymeric molecules is reversed periodically to cause the polymeric molecule to hover in an elongated state. Bensimon also does not teach the limitations of claims 49, 57 and 65-70 as recited below.

With regard to claim 10, 32, 50, Chen teaches an embodiment of claim 1, 25, 48, including the step of periodically reversing the laminar flow to cause the polymeric molecule to hover in an elongated state (col. 40, lines 41-67, where the movement of charged polymers such

as DNA can be controlled through the application of an electric field and the flow can be reversed to assist in stretching of the polymer).

With regard to claim 11, 33, 51, Chen teaches an embodiment of claim 10, 32, 50, wherein the laminar flow is periodically reversed at a rate from between 0.2-5 Hz (col. 40, lines 41-67, where the movement of charged polymers such as DNA can be controlled through the application of an electric field and the flow can be reversed to assist in stretching of the polymer).

With regard to claim 20, 42, Chen teaches an embodiment of claim 17, 39, wherein step (c) includes the step of applying an electrostatic field across the width of the micro-channel to cause adsorption of the polymeric molecule to one wall of the micro-channel (col. 40, lines 41-67, where the movement of charged polymers such as DNA can be controlled through the application of an electric field and the flow can be reversed to assist in stretching of the polymer).

With regards to claim 49, Chen teaches an embodiment of claim 48 further including the step of controlling the flow of liquid to elongate the molecules and separate the elongated molecules by their relative speeds within the laminar flow (col. 17-18, where the elongated molecules are analyzed with regard to their relative speed or 'center of mass' velocity within the flow of the apparatus of the invention; see col. 15, lines 41-52, where the invention provides structures for the stretching and elongation of polymers).

With regards to claim 65, Chen teaches an embodiment of claim 48 further including the step of controlling the flow of liquid to cause elongation only of the polymeric molecules of a

predetermined molecular weight range within the laminar flow (col. 38, lines 10-21, where the size of molecules of interest range from several kilobases to at least a megabase of DNA).

With regards to claim 67, Chen teaches an embodiment of claim 65 further including the step of controlling the flow of liquid to separate the elongated and unelongated molecules as a function of their differing speed within the laminar flow and to separate the elongated molecules from the unelongated molecules by their different speeds in the laminar flow (col,. 37, Figure 23, where polymers of a particular length remain elongated, while polymers of a different length recoil and are no longer elongated and these molecules traverse different and separate paths in the substrate).

With regards to claim 68, Chen teaches an embodiment of claim 65 further including the step of obtaining a digital image of the elongated and unelongated molecules and separating them by image processing (col. 45, lines 10-39, Example 1, where digital images were obtained and both elongated and unelongated molecules were analyzed).

With regards to claim 70, Chen teaches an embodiment of claim 48 further including the step of controlling the flow of liquid to separate the molecules as a function of their propensity to be adsorbed as a function of their length while moving in the laminar flow (col,. 37, Figure 23, where polymers of a particular length remain elongated, while polymers of a different length recoil and are no longer elongated and these molecules traverse different and separate paths in the substrate).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Bensimon and Kambara to incorporate the additional methods of polymer stretching and elongation of Chen to arrive at the claimed

invention with a reasonable expectation for success. Bensimon, Kambara and Chen disclose methods that are directed to the separation, elongation and analysis of polymers as they pass through a microchannel passageway. Regarding the issue of reversing the flow of the passage of the polymeric molecules, as taught by Chen, "the movement of the polymer is controlled, for charged polymers such as DNA, by setting up an electric field which acts on the charges on the polymer… and the polymer follows the electric field lines". Chen also teaches "in addition, with an appropriately charged wall surface, the electro-osmotic flow can be reversed to provide viscous forces which assist the osmotic stretching" (col. 40, lines 41-67). While Bensimon does disclose a charged surface, and the control of the liquid flow, there is no specific teaching of an attempt to reverse the flow of the liquid, or to include an electrical field as an additional level of control of fluid flow and elongation of the polymers. However, as Chen teaches that the flow can be reversed and assist stretching, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the additional steps of reversing the flow as taught by Chen into the method of elongation, separation and alignment taught by Bensimon with a reasonable expectation for success.

Furthermore, it would have been prima facie obvious to have extended the teachings of Bensimon to incorporate the additional methods of polymer stretching and elongation of Chen to arrive at the claimed invention with a reasonable expectation for success. Both Bensimon and Chen disclose methods that are directed to the separation, elongation and analysis of polymers as they pass through a microchannel passageway. Regarding the separation of molecules according to their relative speeds in the laminar flow, as taught by Chen, "the present invention also provides methods and structures that allow polymers of any length, including nucleic acids

containing entire genomes, to be stretched or elongated for further analysis, e.g., determination of their velocities and lengths. Polymers are loaded into a device and run through the structures, propelled by, inter alia, physical, electrical or chemical forces" (col. 15, lines 41-52). These teachings generally address the issue of control of the flow and the speed of the molecules. Chen also states that their method addresses "a need for more accurate methods for determining the length of single elongated polymers and/or determining the length of single elongated polymers and/or distances between landmarks on single elongated polymers". Therefore, while both Chen and Bensimon teach methods directed to the characterization of polymers, specifically DNA, Chen addresses the method from a different perspective than Bensimon, specifically aimed at the analysis of single molecules relative to their length and their velocity. Considering the combined teachings of these references, one of ordinary skill in the art at the time the invention was made would have been motivated to apply the techniques of analyzing and separating elongated polymers based on their velocities within the laminar flow as taught by Chen with a reasonable expectation for success.

Response to Arguments

Applicant's arguments filed April 16, 2008 have been fully considered but they are not persuasive.

Applicant traverses the priority assertion made above regarding claims 10-16, 32-38 and 50-56. However, Applicant provides no explicit arguments regarding the explicit support for these claims in the priority documents. Therefore, these arguments are not persuasive and the priority awarded to the claims remains the same as asserted above.

Applicant traverses the rejection and asserts that "the pending claims are directed towards methods of elongating polymeric molecules by using only laminar flow. In contrast, Schwartz I and Schwartz II claim methods of preparing nucleic acid molecules elongated and fixed for manipulation by depositing such molecules on a planar surface having a positively charged surface". Applicant asserts that while both disclose laminar flow devices (e.g., Figure 25), "neither disclosed using only laminar flow with these devices for elongating nucleic acid molecules" (p. 15).

Applicant also asserts that "the Examiner has identified no passage in either patent disclosing, suggesting or hinting at this fundamentally different approach" (p. 15 of remarks).

These arguments are not persuasive. Applicant's arguments regarding the restriction to only laminar flow in the instant claims is acknowledged. However, the claims of the '074 patent (Schwartz I) and '158 patent (Schwartz II) claim the elongation and fixation of nucleic acid molecules. Elongation and fixation (as claimed, for example in claims 1 and 17 of the instant claims) achieved specifically with laminar flow as in the instant claims is rendered obvious by the limitations of the copending claims which recite elongation and fixation. Stated in another way, laminar flow falls within the scope of "elongation and fixation" as claimed in the cited copending patents and therefore the copending claims are an obvious variant of the instantly claimed invention.

Furthermore, while Applicant is correct that passages of the patent disclosures are not addressed in the substance of the rejection, the rejection is based on the claims. Furthermore, Applicant incorrectly asserts that laminar flow is not mentioned in either disclosure. For

example, in 6,509,158, "the single nucleic acid molecules are elongated via flow-based techniques. In such an embodiment, a single nucleic acid molecule is elongated, manipulated (via, for example, a regio-specific restriction digestion), and/or analyzed in a laminar flow elongation device. The present invention further relates to and describes such a laminar flow elongation device" (col. 3, lines 58-64). Laminar flow is also disclosed as being useful for elongation at columns 19-21 of the '158 patent. Therefore, the arguments asserted above are not persuasive and the rejections are maintained.

Applicant traverses the rejection of claims 1-7, 25-31, 48 and 62-64 under 35 USC 102 as being anticipated by Kambara et al. (5,356,776). Applicant asserts that "Kambara used fluid flow associated with electrophoresis (presumably sheath flow, electroosmotic flow and capillary/convective flow) to manipulate the molecules". Applicant points to a variety of passages and figures in Kambara asserting that Kambara only separates and elongates polymers using electrophoresis. Applicant also asserts "the same holds for Kambara's methods for elongating polymeric molecules attached to particles in fluid flow associated with electrophoresis" (p. 17 of remarks).

These arguments are not persuasive. First, it is noted that the instant specification does not explicitly define the term laminar flow. Therefore, the term is being given a broad interpretation as reading on instances where fluid or liquid flow is applied to a polymer for elongation or stretching. Applicant is mischaracterizing the teachings of Kambara in the above arguments. While Kambara does teach embodiments where the polymers are separated specifically by electrophoresis, Kambara teaches electrophoresis in the alternative to separation

by fluid flow. Specifically, as stated at col. 3, lines 48-57, Kambara teaches "To achieve the objects of the present invention, another process binds a label to one terminus of DNA, fixes the other terminus to a matrix physically or chemically, stretches the DNA by means of electric fields **or liquid flow** and detects the position of the terminus bound to the label to measure the length of the DNA" (emphasis added). Therefore, Applicant's arguments regarding Kambara are incorrect, Kambara does teach elongation and stretching of the polymers through liquid flow and does not imply that the liquid flow is a part of the electrophoresis. Kambara explicit teaches electrophoresis separation or fluid-flow mediate separations as two distinct and separate alternatives. Therefore, for these teachings, Kambara anticipates the instantly claimed invention.

Furthermore, regarding Example 4, Applicant states that the polymeric molecules are fixed at one end and elongated by electrophoresis. However, at col. 10, lines 48-67, referring to Figure 4, Kambara states "The DNA can pass one of the apertures 106 except its portion bound to the particle 103, which allows one terminus of the DNA to be fixed in a specific position. Applying electric fields between electrodes 105a and 105b **or using liquid flow causes DNA to migrate, fixes the particle 103 at the mouth of the apertures and stretches the DNA**. (emphasis added)." Again, Kambara clearly states that either electrophoresis OR fluid flow can be used to elongate and stretch the DNA and does not imply that the fluid flow is a direct result of electrophoresis. Therefore, Applicant's arguments regarding Kambara are not persuasive and the rejection is maintained.

Applicant traverses the rejection of claims 8-9, 17-18, 21-24, 39-41, 43-46 and 58-61 under 35 U.S.C. 103 as obvious over Kambara and Bensimon. Applicant asserts "at best,

Kambara teaches arguendo that polymeric molecules can be elongated, aligned or separated by electrophoresis or by non-laminar fluid flow resulting from electrophoresis". Regarding Bensimon, Applicant argues "Bensimon does not cure the deficiencies of Kambara and provides the skilled artisan with no motivation to combine with Kambara." Applicant also asserts "Bensimon does not disclose using laminar flow to elongate, align or separate polymeric molecules during passage through a microchannel" (p. 19 of remarks).

These arguments are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

For the reasons stated above Kambara is relied upon for the teaching of separation using fluid flow or laminar flow and does not only teach separation using electrophoresis or the application of electric fields. Bensimon is not relied upon in any way for a teaching of laminar flow separation. Bensimon is relied upon for elongation of the molecules, alignment of the molecules and fixation onto the wall of the microchannel. While Bensimon may not teach that the method is practiced using laminar flow, the elements of Bensimon are still properly combinable with the teaching of Kambara. The rejection is maintained.

Applicant traverses the rejection of claims 10-16, 20, 32-38, 42, 49-57 and 65-70 as obvious over Kambara, in view of Bensimon and Chan. Applicant repeats the assertions stated above regarding Kambara and Bensimon. Regarding Chan, Applicant asserts "Chan did not

disclose laminar flow to elongate, align, or separate polymeric molecules during passage through a microchannel for subsequent analysis. Because Chan failed to disclose these elements, it cannot render the pending claims obvious" (p. 20 of remarks). Applicant also asserts "Chan used an electrical field to move polymeric molecules in a fluid. In fact, Chan noted that the electrical field should 'not necessarily [act] on the surrounding fluid at all (if it is uncharged)'" (p. 20 of remarks).

These arguments are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant again argues that neither Kambara, Bensimon or Chan teaches separation or elongation of polymers using laminar flowing liquid. These arguments are not persuasive because neither Bensimon or Chan are relied upon for a teaching of laminar separation or elongation of polymeric molecules. This element of the claimed invention is anticipated by the teaching of Kambara for the reasons stated in the art rejection and reiterated and clarified above in the response to Applicant's arguments. So, Applicant's arguments against elements for which Bensimon and Chan are not relied upon are misdirected and are not persuasive. The rejections are maintained for the reasons stated above.

Conclusion

No claims are allowed.

Claims 19 and 41 are free of the prior art. The closest prior art, Bensimon does not teach the application of an acceleration across the width of the microchannel. These claims stand rejected for other reasons as stated above.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie K. Mummert, Ph.D. whose telephone number is 571-272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Examiner, Art Unit 1637

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/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637